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ORIGINAL PAPER

QM study and conformational analysis of an isatin Schiff base as a potential cytotoxic agent

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Abstract Isatin is an important compound from the biological aspect of view. It is an endogenous substance and moreover; various pharmacological activities have been reported for isatin and its derivatives. In-vitro cytotoxic effects of the prepared isatin Schiff bases toward HeLa, LS180 and Raji human cancer cell lines has been reported in our previous work. 3-(2-(4-nitrophenyl)hydrazono) indolin-2-one was found to be the most potent one among the studied compounds (IC_{30}=12.2 and 21.8 μM in HeLa and LS-180 cell lines, respectively). Obtained biological data could be well interpreted using docking binding energies toward vascular endothelial growth factor receptor (VEGFR-2); a key anticancer target being biologically investigated against various isatin derivatives. In the present work, quantum mechanical (QM) method including functional B3LYP in association with split valence basis set using polarization functions (Def2-SVP) was used to estimate individual ligand-residue interaction energies for the docked 3-(2-(4-nitrophenyl)hydrazono) indolin-2-one into VEGFR-2 active site. Results were further interpreted via calculated polarization effects induced by individual amino acids of the receptor active site. A fairly good correlation could be found between polarization effects and estimated binding energies (R^2=0.7227). Conformational analysis revealed that 3-(2-(4-nitrophenyl) hydrazono) indolin-2-one might not necessarily interact with the VEGFR-2 active site in its minimum energy conformation.

Keywords B3LYP · Conformational analysis · Cytotoxicity · Isatin · Quantum mechanical

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Introduction

Isatin is a natural product found in a number of plants including those of the genus *Isatis* [1]. It has also been found as a metabolic derivative of adrenaline in humans [2]. Moreover, it has been demonstrated that isatin is found at higher levels in patients involved with neuropathological conditions and also proved to be a competitive MAO-B inhibitor [3, 4]. Various derivatives of isatin are known to possess a range of pharmacological properties including antiprotozoal [5, 6], antiglycation [7], anticonvulsant and sedative-hypnotic [8, 9], anti-inflammatory [10], antibacterial and anti-fungal [11] activities. Thus isatin is a biologically validated starting point for the design and synthesis of chemical libraries directed at these targets [12]. Due to the privileged nature of isatin, libraries designed and synthesized around the basic structure of this scaffold may yield medicinally active compounds with high hit rates.

In a typical lead/drug discovery protocol, potential candidate molecules may suffer from undesirable properties in their pharmacokinetic and pharmacodynamic profiles. Structure-based drug design has been considered as one of the major strategies in achieving potential drug candidates [13, 14]. In lead-drug development strategies, combination of experimental methods with computer aided molecular design (CAMD) techniques is essential for the development of new drugs aimed at new targets, and thus for medicinal chemistry [15].